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Early View

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Air pollution exposure and lung function until age 16: The PIAMA birth cohort study

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Take home message

Exposure to air pollution may be associated with increased airway obstruction but not reduced lung volume until age 16.

Abstract

Evidence for effects of air pollution exposure on lung function growth into adolescence is scarce. We investigated associations of air pollution exposure with lung function and lung function growth until age 16.

We conducted longitudinal (N=915) and cross-sectional analyses (N=721) of associations of air pollution exposure with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) growth from ages 8 to 16 and FEV_1 and FVC at age 16. We estimated residential concentrations of nitrogen dioxide (NO_2), "soot", and particulate matter with diameters < 2.5 ($PM_{2.5}$), < 10 (PM_{10}), and 2.5−10 μm (PM_{coarse}) during the preschool, primary school and secondary school time windows by land use regression models and analysed associations with (growth in) FEV_1 and FVC by linear (mixed effects) regression.

Higher air pollution exposure was associated with reduced FEV_1 growth, [e.g. adjusted difference (95% confidence interval) -0.26% (-0.49 to -0.03%) per interquartile range increase in secondary school $PM_{2.5}$] and lower FEV_1 [-2.36% (-3.76 to -0.94%)], but was not adversely associated with FVC. Associations with FEV_1 were stronger in boys than girls and were not modified by asthma status.

Higher air pollution exposure may lead to increased airway obstruction, but not reduced lung volume in adolescence.

Keywords: air pollution, lifetime exposure, lung function**,** epidemiology

Introduction

Air pollution exposure has been shown to adversely affect respiratory health of children [1]. The role of air pollution exposure in lung function growth has also been determined [2-5]. However, effects of air pollution exposure over the whole lifetime have rarely been investigated. Understanding the effects of lifetime air pollution exposure on health can provide essential insights into the relevance of exposure during different time windows and provide guidance on the timing and structure of interventions to successfully improve respiratory health [6].

Until now, mainly air pollution exposure during distinct age ranges has been investigated. Several studies in children and adolescents aged 8-16 years [7-10] reported adverse associations of exposure with lung function within first three years of life, while a recent multi-cohort study reported associations with exposures between 6-8 years [11].

There are currently few longitudinal studies of the association between air pollution exposure and lung function in adolescence [2, 10, 12]. The Children's Health Study (CHS) [2, 5] in Southern California has presented strong evidence for an association between air pollution exposure and lung function growth from 10–18 years. Higher exposure from study entry (~10 years) was associated with reduced growth in FEV_1 by age 18 [2]. Similarly, the Swedish Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) study [10], reported an association between early life air pollution exposure and lower lung function at age 16.

Lung function reaches its maximum in early adulthood. Reduced growth resulting in low maximum attained level of lung function in early adulthood, may be associated with an increased risk of developing chronic obstructive pulmonary disease later in life [13, 14]. This makes research on persistence of air pollution effects since birth an essential health interest.

We therefore investigated associations of air pollution exposure from birth with lung function growth from ages 8 to 16 and lung function at age 16. Since differences in associations of air

pollution with lung function have been suggested between boys and girls and between asthmatics and non-asthmatics [2, 7, 12], we also explored possible effect modification by sex and asthma status. Currently, evidence for potential interactions with sex and asthma status is mixed and therefore, there is no expected direction for these interactions.

Methods

Study design and study population

This study was performed within the Dutch population-based Prevention and Incidence of Asthma and Mite Allergy birth cohort study (PIAMA) [15]. Briefly, pregnant women were recruited in 1996/1997 from northern, western and central regions of the Netherlands. The cohort started with 3963 new-borns. Data on lifestyle, household and health characteristics were collected through questionnaires completed by parents during pregnancy, at 3 months, annually till age 8, and at ages 11, 14, and 16. At ages 8, 12 and 16, lung function was measured as part of medical examinations. The current study populations consist of participants with air pollution exposure data and a) at least two lung function measurements throughout follow-up for longitudinal analyses (N=915) and b) lung function measurements at age 16 for cross-sectional analyses (N=721, Figure S1). Ethical approval was obtained from ethical review boards of participating institutes and written informed consent was obtained from participants as well as their parents/legal guardians.

Lung function measurements

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured by spirometry at ages 8, 12 and 16. At ages 8 and 12, 1058 and 1292 participants from all

three regions of the country had successful lung function measurements, respectively. At age 16, participants from northern and central regions of the Netherlands (N=2159) were invited for medical examination. Successful lung function measurements were obtained in 721. We used Jaeger pneumotachograph (Viasys Healthcare, USA) at age 8 and Easy One spirometers (NDD Medical Technologies, Inc, Switzerland) at age 12. Both Jaeger Masterscreen pneumotachograph (CareFusion, Yoba Linda, CA, USA) and the EasyOne spirometer were used at age 16. All measurements were performed following recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [16]. For each participant, at least three acceptable manoeuvres were required. In addition, test results were included, which did not meet these criteria (difference between the largest and next largest value ≤ 150 mL for FEV_1 and FVC), but which were obtained from otherwise technically acceptable flow-volume curves with differences between the largest and next largest values for FEV_1 and FVC ≤ 200 mL, (N=190 at age 12 and N=76 at age 16), as in previous analyses [17]. Since different spirometers were used at age 16, we compared the spirometers in 49 volunteers in a separate experiment and calibrated measurements performed with the EasyOne spirometer using regression equations obtained from the comparison:

$$FEV_1 Masterscreen = 0.114\ (0.05) + 1.032\ (0.01) * FEV_1 EasyOne$$

$$FVC Masterscreen = 0.357\ (0.05) + 1.005(0.01) * FVC EasyOne$$

Air pollution exposure assessment

We used land use regression models (LUR) to estimate annual average concentrations of nitrogen dioxide (NO_2) , particulate matter with aerodynamic diameters of < 2.5 µm ($PM_{2.5}$), < 10 µm (PM_{10}), and 2.5-10 µm (PM_{coarse}), and $PM_{2.5}$ absorbance (“soot”, defined as reflectance of $PM_{2.5}$ filters) at the participants’ home addresses throughout follow-up as

described elsewhere [18, 19]. Concisely, three two-week measurements of nitrogen dioxide (NO_2) were performed at 80 sites in the study area between October 2008 and February 2010. Simultaneous measurements of $PM_{2.5}$, PM_{10}, $PM_{coarse,}$ and $PM_{2.5}$ absorbance were performed at 40 of these sites. The three measurements were averaged to obtain the annual average concentration for each site [20, 21]. Variables such as nearby traffic, household density, and land use derived from Geographic Information Systems (GIS) were used as predictor variables in LUR model development [18, 19]. Substantial variability in annual average concentrations was explained for NO_2, $PM_{2.5}$, $PM_{10,}$ and $PM_{2.5}$ absorbance (R^2_{LOOCV}=0.61–0.89), but not for PM_{coarse} (R^2_{LOOCV} =0.38) [18, 19].

We used complete residential histories from birth until the 16-year lung function measurements to estimate average air pollution exposures during different time windows: preschool (birth–4 years), primary school (5–12 years), and secondary school (13–16 years). Participant's occupancy at an address was used as weight in calculation of time window-specific average concentrations.

Confounding variables

Information on potential confounders was obtained from parental-completed questionnaires. The following set of *a priori* selected potential confounders was considered: age, sex, weight, height, parental education (maximum of either maternal or paternal education), maternal and paternal atopy, breastfeeding, respiratory infections in the last 3 weeks before lung function measurement, Dutch nationality (both parents born in the Netherlands), maternal smoking during pregnancy; indoor tobacco smoke exposure in the home, furry pets in the home, moulds in the home, gas cooking during the first year of life; and average air pollution

concentrations during the 7 days preceding lung function measurements retrieved from the Dutch National Air Quality Monitoring Network.

Statistical analysis

Longitudinal analyses of lung function growth from ages 8 to 16: We used linear mixed effects models with random subject intercepts and exposure-age interaction terms to assess associations of air pollution exposure with lung function growth from ages 8 to 16. The interaction terms can be directly interpreted as the association of air pollution exposure with annual rate of change in lung function. Only the preschool time window was used in longitudinal analyses to ensure that exposure precedes outcome.

Cross-sectional analyses of lung function at age 16: We used linear regression to assess associations of air pollution exposure with lung function at age 16. Associations with exposure during different window were assessed in separate models.

Lung function was log-transformed in all analyses because of the strongly non-linear relationships between lung function, age, height and weight [22, 23]. Associations with different pollutants were assessed in separate models with concentrations as continuous variables assuming a linear dose-response relationship without threshold. Both longitudinal and cross-sectional analyses were initially adjusted for sex, age, log transformed height and weight at time of lung function measurements; and then additionally adjusted for all other potential confounders. Associations are presented as percent differences in lung function and 1-year lung function growth for an interquartile range (IQR) increase in exposure to facilitate comparison of estimates between pollutants. The same IQRs were used in all analyses. Percent differences were calculated from estimated regression coefficients β as $(e^{\beta \times IQR} - 1)$

×100. We performed complete case analyses and excluded 44 and 50 participants, respectively, with missing data for one or more potential confounders from additionally adjusted longitudinal and cross-sectional analyses. Results of crude analyses did not differ between all participants and the subset with complete information of all potential confounders (data not shown).

Sensitivity analyses

We performed stratified analyses by sex and asthma status. We also explored the independence of associations of exposure during different time windows in movers with lung function at age 16 using multi-time window models. We only included preschool and secondary school time window exposures in one model because models with other combinations of time windows led to multicollinearity problems (Variance Inflation Factors >3). All analyses were performed using SAS V9.4 (Cary, USA) with significance levels of 0.05.

Results

Population characteristics

Study population characteristics for longitudinal and cross-sectional analyses and distributions of lung function variables are presented in Table 1. More than 60% of the participants had at least one highly educated parent, more than 30% had an atopic father and more than 30% had an atopic mother. Twenty percent of the participants were exposed to indoor tobacco smoke exposure in the home in early life. At age 16, the mean (SD) was 3.9 (0.7) L for FEV_1 and 4.7 (0.8) L for FVC (Table 2). Characteristics of study populations and the PIAMA baseline

cohort were generally similar, except for a higher percentage of participants with an atopic mother in the longitudinal analysis population and higher percentage of highly educated parents in both study populations (Table S1). Sixty-two percent of the participants changed addresses (movers) at any time between preschool time window and the 16-year lung function measurements. Population characteristics were not different between movers and non-movers (Table S2).

Air pollution exposure

The distributions of estimated average air pollution levels for longitudinal and cross-sectional analyses populations were similar (Tables 3 and S3). Air pollution levels were consistent between time windows with means slightly decreasing over time for NO_2 and $PM_{2.5}$ absorbance. Consequently, exposure during secondary school time window was slightly lower than exposure during preschool time window in movers (Table S4). Variation in exposure levels was larger for NO_2 and $PM_{2.5}$ absorbance than for PM mass. NO_2, $PM_{2.5}$ absorbance, $PM_{2.5}$ and PM_{10} concentrations were moderately to highly correlated within time windows (r=0.53–0.96, Tables S5 and S6). Moderate to high correlations were also observed for concentrations of the same pollutant between time windows (r=0.65–0.96) and these correlations were similar for movers (r=0.48–0.95, Table S7).

Longitudinal analyses of lung function growth from ages 8 to 16

Exposure during preschool time window was associated with reduced growth in FEV_1 for all pollutants, e.g. difference in 1-year growth in FEV_1 (95 % confidence interval) was -0.31% (-0.47 to -0.14%) per 7.8 $\mu g/m^3$ increase in NO_2 and -0.26% (-0.49 to -0.03%) per 1.2 $\mu g/m^3$

increase in $PM_{2.5}$. Growth in FVC was not associated with air pollution exposure except for a positive association with $PM_{2.5}$ [0.24% (0.03 to 0.45%) per 1.2 µg/m^3] (Table 4).

Cross-sectional analyses of lung function at age 16

Figure 1 and Table S8 show associations of FEV_1 and FVC at age 16 with air pollution exposure. We observed lower FEV_1 at age 16, with higher air pollution exposure e.g. percent difference (95% confidence interval) was -2.14% (-3.53 to -0.73%) per 1.2 µg/m^3 increase in preschool $PM_{2.5}$ and -1.29% (-2.31 to -0.26%) per 0.9 µg/m^3 increase in secondary school PM_{10}. Association estimates were consistently negative for FVC at age 16, but none of the associations was statistically significant, e.g. -0.63% (-1.68 to 0.44%) per 0.3 10^{-5}/m increase in primary school $PM_{2.5}$ absorbance and -0.64% (-1.54 to 0.26%) per 0.5µg/m^3 increase in secondary school PM_{coarse}.

Sensitivity analyses

Negative associations of air pollution exposure with FEV_1 growth and FEV_1 at age 16 were stronger in boys than in girls, whereas associations with FVC were negative in boys and mostly positive in girls (Figure 2, Tables S9 and S10). Associations of air pollution with FEV_1 and FVC (growth) were not significantly different between asthmatics and non-asthmatics, but positive estimates for FEV_1 in asthmatics at age 16 were observed (Figure 2, Tables S9 and S11). Analyses with mutual adjustment of time windows showed lower $FEV_{1,}$ with higher air pollution exposure mainly with secondary school time window exposure but estimates were attenuated for the preschool time window (Table S12).

Discussion

In the PIAMA birth cohort, we found that higher air pollution exposure from birth until age 16 was associated with reduced FEV_1 growth from age 8 to 16 and lower FEV_1 at age 16, but not with reduced FVC and FVC growth.

Our findings concur with longitudinal studies that have reported associations of air pollution exposure with reduced lung function growth. The longitudinal CHS from the USA has demonstrated reduced lung function growth with increasing air pollution exposure in adolescents [2, 5]. Over an 8-year period, exposure to NO_2 and $PM_{2.5}$ was associated with reduced growth in FEV_1 and FVC [2]. However, the CHS assessed exposure from study entry (~10 years) and not exposure from birth. The Swedish BAMSE cohort study [10] addressed this gap and found that exposure to nitrogen oxides (NO_x) and PM_{10} at the participants' home addresses during the first year of life was not associated with reduced lung function growth in contrast to our findings.

This study and the BAMSE study are, to our knowledge, the only two studies that have studied the association of air pollution exposure from birth to adolescence with lung function growth into adolescence. More longitudinal studies are warranted to confirm and add to these findings. Better understanding of effects of air pollution exposure on subsequent lung function growth extending into adolescence and adulthood is imperative for preventive and management strategies in reducing the burden of respiratory diseases [24].

Associations of air pollution exposure with lung function have been reported in several studies in pre- and primary school children aged 5-11years followed from birth [7-9, 11, 25], but analyses linking air pollution exposure to lung function until adolescence are scarce. A recent BAMSE study investigated the association of air pollution exposure from birth into adolescence and lung function in adolescents and reported associations of traffic-related air pollution exposure during the first year of life with lower FEV_1 at age 16, but not during later

time periods [10]. The German GINI/LISA study [12] performed a similar analysis and reported no association of air pollution exposure at birth, 10 and 15-year addresses with lung function at 15 years, in contrast to our study. We previously reported that higher exposure to air pollution at the current address was associated with lower FEV_1 at ages 8 [11] and 12 [17], which suggests the importance of mid-childhood exposures in our cohort. Possibilities to compare air pollution concentrations between studies are limited as different methods have been used in different studies. However, comparisons can be made for the Swedish BAMSE and German GINI/LISA cohorts, because exposures have been estimated using a standardized methodology recently. Compared to the Netherlands, air pollution levels in Sweden, are considerably lower but the Dutch concentrations are comparable to those measured in Germany [11]. Comparison of pollutant concentrations with other studies such as CHS is not straightforward because different exposure assessment methods were used. The present findings extend into adolescence and add that air pollution exposure has an impact on lung function until adolescence. Together with findings of the BAMSE study, our results strengthen the conclusions of a recent review that air pollution exposure in early life, later life and exposure over the entire age range could be relevant [26].

We found higher air pollution exposure to be associated with lower FEV_1 and reduced growth in FEV_1, but no indication for an adverse effect on FVC. This has also been observed in other studies [7, 27, 28]. Our results suggest that air pollution exposure affects the diameter of the airways and hence increases airway obstruction, but does not affect lung volume. However, current evidence is not sufficient to conclude that the effects of air pollution are limited to specific spirometric measures [29].

We observed associations of air pollution exposure with both reduced FEV_1 growth and lower FEV_1 in boys, but not in girls, consistent with CHS and BAMSE findings [2, 10]. Literature suggests that boys already present with a higher total number of alveoli and alveolar surface

area at birth than girls and that boys may have a pulmonary phenotype more susceptible to adverse effects of air pollution exposure since they have narrower airways between infancy and adolescence [30]. The current literature however, is inconsistent with regard to a possible air pollution-sex interaction as a number of studies in children have shown stronger associations of air pollution and lung function in girls [7, 31] and other studies have found no differences [12, 25]. Results of these studies are summarized in Tables S13. We observed reduced FEV_1 growth in asthmatics and non-asthmatics and lower FEV_1 with increasing air pollution exposure in non-asthmatics but not in asthmatics; differences, however, were not statistically significant. Associations with air pollution tended to be negative for FVC and FVC growth in both, asthmatics and non-asthmatics. Although stronger negative associations with FEV_1 in non-asthmatics than in asthmatics have been reported previously in the CHS and BAMSE cohorts [5, 10], we need to acknowledge that our study had few asthmatics and therefore was possibly underpowered to identify significant differences by asthma status. Earlier reports on interactions between air pollution and asthma are inconsistent (Table S13). Most studies that investigate effect modification by asthma are likely underpowered to detect a difference and literature seldom reports consistent stronger or weaker associations in asthmatics [26].

In mutually adjusted time window analyses, associations with exposure during the secondary school time window were more pronounced than associations with preschool exposure, suggesting that later life exposure could play a key role in the level of lung function of adolescents in our study.

An important strength of our study is availability of repeated objective measurements of lung function and detailed individual exposure data from birth, allowing us to investigate effects of lifetime exposure. We also consider analysis of lung function growth into adolescence with

exposure from birth as a major strength as to the extent of our knowledge, only one other study [10] has done this.

This study also has several important limitations. Two different spirometers were used to measure lung function during the 16-year medical examination. We acknowledge that systematic differences between measurements obtained by the two spirometers may affect the estimated air pollution exposure-lung function relationships. We therefore conducted a separate experiment in healthy volunteers and derived calibration equations to correct for systematic differences. The correlation between the readings from the two instruments was very high (0.98-0.99) and the calibration factor was estimated with great precision so that after calibration, the impact of the use of different instruments on our findings is likely small.

We used spatial exposure models based on an air pollution measurement campaign performed in 2008–2010 to assess air pollution exposure from 1996/1997 (when children were born) until 2013/2014 when 16-year lung function measurements were conducted assuming constant spatial contrasts in air pollution levels since birth. Several studies have demonstrated the validity of LUR models over several years [32-34] supporting our assumption of constant spatial contrasts. In addition, measurement data from the Dutch National Air Quality Monitoring Network also show that annual average concentrations of NO_2 and PM_{10} have not changed substantially between 2000 and 2007 [35]. We did not account for long-term temporal trends in air pollution levels since the beginning of the cohort. Therefore, the stronger associations with more recent exposure than with early life exposure could be partly attributed to measurement error which may be larger for early life exposures because of larger time difference with the LUR models measurement campaign.

Another limitation is that we used estimated residential exposure disregarding other sources exposures e.g. school address exposures. The correlation between home and school address exposures, however, was moderate to high for NO_2, $PM_{2.5}$, $PM_{2.5}$ absorbance and PM_{10} in our

cohort (r=0.68–0.88 for primary school exposure and r=0.36–0.73 for secondary school exposure, Table S14). Therefore, measurement error resulting from reliance on residential exposure is likely small.

We acknowledge the difficulty to disentangle effects in the different time windows because pollution levels during the different time windows were correlated. Therefore, effects of exposure in later life may reflect effects from earlier life exposures. We however, attempted to disentangle preschool from secondary school time window exposures in movers and results suggested a greater importance of later life exposures for lung function in adolescence.

The prevalence of maternal atopy was higher in the longitudinal study population than in the source population due to overrepresentation of children of atopic mothers invited for lung function measurements at age 8. There were also more children from highly educated parents in the study population compared to the baseline PIAMA population, which may limit generalizability of our findings to the full PIAMA cohort and to the general population.

In conclusion, higher air pollution exposure may lead to increased airway obstruction, but not to reduced lung volume in adolescence. We contribute to limited knowledge on the potential impact of air pollution exposure on lung function development throughout childhood into adolescence.

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REFERENCES

1. Gotschi T, Heinrich J, Sunyer J, Kunzli N. Long-term effects of ambient air pollution on lung function: a review. *Epidemiology* 2008; 19: 690-701.

2. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057-1067.

3. Gauderman WJ, Gilliland GF, Vora H, Avol E, Stram D, McConnell R, Thomas D, Lurmann F, Margolis HG, Rappaport EB, Berhane K, Peters JM. Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002; 166: 76-84.

4. Gauderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, Margolis HG, Peters J. Association between air pollution and lung function growth in southern California children. *Am J Respir Crit Care Med* 2000; 162: 1383-1390.

5. Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; 369: 571-577.

6. Berkman LF. Social epidemiology: social determinants of health in the United States: are we losing ground? *Annu Rev Public Health* 2009; 30: 27-41.

7. Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker SE, Nafstad P. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008; 19: 129-137.

8. Molter A, Agius RM, de Vocht F, Lindley S, Gerrard W, Lowe L, Belgrave D, Custovic A, Simpson A. Long-term exposure to PM10 and NO2 in association with lung volume

and airway resistance in the MAAS birth cohort. *Environ Health Perspect* 2013; 121: 1232-1238.

9. Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, Svartengren M, Melen E, Pershagen G. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. *Am J Respir Crit Care Med* 2012; 186: 1286-1291.
10. Schultz ES, Hallberg J, Bellander T, Bergstrom A, Bottai M, Chiesa F, Gustafsson PM, Gruzieva O, Thunqvist P, Pershagen G, Melen E. Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence. *Am J Respir Crit Care Med* 2016; 193: 171-177.
11. Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, Eeftens M, Flexeder C, Fuertes E, Heinrich J, Hoffmann B, de Jongste JC, Kerkhof M, Klumper C, Korek M, Molter A, Schultz ES, Simpson A, Sugiri D, Svartengren M, von Berg A, Wijga AH, Pershagen G, Brunekreef B. Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect* 2013; 121: 1357-1364.
12. Fuertes E, Bracher J, Flexeder C, Markevych I, Klumper C, Hoffmann B, Kramer U, von Berg A, Bauer CP, Koletzko S, Berdel D, Heinrich J, Schulz H. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: The GINIplus and LISAplus cohorts. *Int J Hyg Environ Health* 2015; 218: 656-665.
13. Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015; 373: 111-122.

14. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szefler SJ, Sharma S, Kho AT, Cho MH, Croteau-Chonka DC, Castaldi PJ, Jain G, Sanyal A, Zhan Y, Lajoie BR, Dekker J, Stamatoyannopoulos J, Covar RA, Zeiger RS, Adkinson NF, Williams PV, Kelly HW, Grasemann H, Vonk JM, Koppelman GH, Postma DS, Raby BA, Houston I, Lu Q, Fuhlbrigge AL, Tantisira KG, Silverman EK, Tonascia J, Weiss ST, Strunk RC. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *N Engl J Med* 2016; 374: 1842-1852.

15. Wijga AH, Kerkhof M, Gehring U, de Jongste JC, Postma DS, Aalberse RC, Wolse AP, Koppelman GH, van Rossem L, Oldenwening M, Brunekreef B, Smit HA. Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol* 2014; 43: 527-535.

16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338.

17. Gehring U, Beelen R, Eeftens M, Hoek G, de Hoogh K, de Jongste JC, Keuken M, Koppelman GH, Meliefste K, Oldenwening M, Postma DS, van Rossem L, Wang M, Smit HA, Brunekreef B. Particulate matter composition and respiratory health: the PIAMA Birth Cohort study. *Epidemiology* 2015; 26: 300-309.

18. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, Declercq C, Dedele A, Dons E, de Nazelle A, Dimakopoulou K, Eriksen K, Falq G, Fischer P, Galassi C, Grazuleviciene R, Heinrich J, Hoffmann B, Jerrett M, Keidel D, Korek M, Lanki T, Lindley S, Madsen C, Molter A, Nador G, Nieuwenhuijsen M, Nonnemacher M, Pedeli X, Raaschou-Nielsen O, Patelarou E, Quass U, Ranzi A, Schindler C, Stempfelet M, Stephanou E, Sugiri D, Tsai MY, Yli-Tuomi T, Varro MJ, Vienneau D,

Klot S, Wolf K, Brunekreef B, Hoek G. Development of Land Use Regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol* 2012; 46: 11195-11205.

19. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, Tsai M-Y, Künzli N, Schikowski T, Marcon A, Eriksen KT, Raaschou-Nielsen O, Stephanou E, Patelarou E, Lanki T, Yli-Tuomi T, Declercq C, Falq G, Stempfelet M, Birk M, Cyrys J, von Klot S, Nádor G, Varró MJ, Dėdelė A, Gražulevičienė R, Mölter A, Lindley S, Madsen C, Cesaroni G, Ranzi A, Badaloni C, Hoffmann B, Nonnemacher M, Krämer U, Kuhlbusch T, Cirach M, de Nazelle A, Nieuwenhuijsen M, Bellander T, Korek M, Olsson D, Strömgren M, Dons E, Jerrett M, Fischer P, Wang M, Brunekreef B, de Hoogh K. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. *Atmospheric Environment* 2013; 72: 10-23.
20. Eeftens M, Tsai M-Y, Ampe C, Anwander B, Beelen R, Bellander T, Cesaroni G, Cirach M, Cyrys J, de Hoogh K, De Nazelle A, de Vocht F, Declercq C, Dėdelė A, Eriksen K, Galassi C, Gražulevičienė R, Grivas G, Heinrich J, Hoffmann B, Iakovides M, Ineichen A, Katsouyanni K, Korek M, Krämer U, Kuhlbusch T, Lanki T, Madsen C, Meliefste K, Mölter A, Mosler G, Nieuwenhuijsen M, Oldenwening M, Pennanen A, Probst-Hensch N, Quass U, Raaschou-Nielsen O, Ranzi A, Stephanou E, Sugiri D, Udvardy O, Vaskövi É, Weinmayr G, Brunekreef B, Hoek G. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 – Results of the ESCAPE project. *Atmospheric Environment* 2012; 62: 303-317.
21. Cyrys J, Eeftens M, Heinrich J, Ampe C, Armengaud A, Beelen R, Bellander T, Beregszaszi T, Birk M, Cesaroni G, Cirach M, de Hoogh K, De Nazelle A, de Vocht

F, Declercq C, Dėdelė A, Dimakopoulou K, Eriksen K, Galassi C, Grąulevičienė R, Grivas G, Gruzieva O, Gustafsson AH, Hoffmann B, Iakovides M, Ineichen A, Krämer U, Lanki T, Lozano P, Madsen C, Meliefste K, Modig L, Mölter A, Mosler G, Nieuwenhuijsen M, Nonnemacher M, Oldenwening M, Peters A, Pontet S, Probst-Hensch N, Quass U, Raaschou-Nielsen O, Ranzi A, Sugiri D, Stephanou EG, Taimisto P, Tsai M-Y, Vaskövi É, Villani S, Wang M, Brunekreef B, Hoek G. Variation of NO2 and NOx concentrations between and within 36 European study areas: Results from the ESCAPE study. *Atmospheric Environment* 2012; 62: 374-390.

22. Dockery DW, Berkey CS, Ware JH, Speizer FE, Ferris BG, Jr. Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. *Am Rev Respir Dis* 1983; 128: 405-412.
23. Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, Speizer FE. Health effects of acid aerosols on North American children: pulmonary function. *Environ Health Perspect* 1996; 104: 506-514.
24. Stocks J, Sonnappa S. Early life influences on the development of chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2013; 7: 161-173.
25. Rice MB, Rifas-Shiman SL, Litonjua AA, Oken E, Gillman MW, Kloog I, Luttmann-Gibson H, Zanobetti A, Coull BA, Schwartz J, Koutrakis P, Mittleman MA, Gold DR. Lifetime Exposure to Ambient Pollution and Lung Function in Children. *Am J Respir Crit Care Med* 2016; 193: 881-888.
26. Schultz ES, Litonjua AA, Melen E. Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children. *Curr Allergy Asthma Rep* 2017; 17: 41.
27. Rosenlund M, Forastiere F, Porta D, De Sario M, Badaloni C, Perucci CA. Traffic-related air pollution in relation to respiratory symptoms, allergic sensitisation and lung function in schoolchildren. *Thorax* 2009; 64: 573-580.

28. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 1997; 8: 298-303.

29. Sunyer J. Lung function effects of chronic exposure to air pollution. *Thorax* 2009; 64: 645-646.

30. Carey MA, Card JW, Voltz JW, Arbes SJ, Jr., Germolec DR, Korach KS, Zeldin DC. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol Metab* 2007; 18: 308-313.

31. Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong H, Jr., Thomas DC. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999; 159: 768-775.

32. Wang R, Henderson SB, Sbihi H, Allen RW, Brauer M. Temporal stability of land use regression models for traffic-related air pollution. *Atmospheric Environment* 2013; 64: 312-319.

33. Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K, Forastiere F. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health* 2012; 11: 48.

34. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med* 2011; 68: 765-770.

35. Beijk R, Mooibroek D, R. H. Air quality in the Netherlands 2007. RIVM report 680704005. Bilthoven, The Netherlands: National Institute for Public Health and the Environment; 2008.

Table 1. Population characteristics for the two study populations.[α]

	Cross-sectional analyses population			Longitudinal analyses population		
Characteristic	**Total (N=721)**	**Boys (N=338)**	**Girls N=(383)**	**Total (N=915)**	**Boys (N=434)**	**Girls N=(481)**
Parental atopy						
Atopic mother, n (%)	232 (32.1)	111 (32.8)	121 (31.5)	434 (47.4)	211 (48.6)	223 (46.3)
Atopic father, n (%)	242 (33.6)	114 (33.7)	128 (33.5)	306 (33.5)	144 (33.1)	162 (33.7)
Boys, n (%)	338 (46.8)			434 (47.4)		
Presence of pets at 3 months, n (%)	302 (41.8)	134 (39.4)	168 (43.8)	409 (44.9)	182 (41.9)	212 (44.0)
Presence of moulds at 3 months, n (%)	193 (27.2)	112 (36.6)	144 (41.5)	243 (27.1)	143 (36.4)	169 (38.9)
Breastfeeding > 12 weeks, n (%)	434 (60.2)	191 (56.5)	243 (63.4)	534 (58.4)	246 (56.6)	288 (59.8)
Gas cooking at 3 months, n (%)	613 (85.3)	281 (83.1)	332 (87.3)	771 (84.7)	355 (82.2)	416 (87.0)
Maternal smoking during pregnancy, n (%)	92 (12.8)	38 (11.3)	54 (14.1)	124 (13.6)	54 (12.5)	70 (14.6)
Indoor tobacco smoke exposure at 3 months, n (%)	146 (20.2)	69 (20.4)	77 (20.1)	192 (20.9)	89 (20.5)	103 (21.4)
Parental education						
Low, n (%)	53 (7.3)	27 (7.9)	26 (6.7)	75 (8.2)	40 (9.2)	35 (7.3)
Intermediate, n (%)	215 (29.8)	97 (28.7)	118 (30.8)	282 (30.8)	127 (29.2)	155 (32.3)
High, n (%)	453 (62.8)	214 (63.3)	239 (62.4)	557 (60.9)	267(61.5)	290 (60.4)
Dutch nationality, n (%)	686 (97.1)	323 (97.3)	363 (96.8)	872 (96.5)	413 (96.0)	459 (96.9)
Asthma at age 16, n (%)	59 (8.5)	32 (9.8)	27 (7.3)	55 (9.1)	29 (10.2)	26 (8.0)
Respiratory infections in the 3 weeks before the lung function measurement						
Age 16, n (%)	303 (42.1)	128 (37.8)	175 (45.7)	266 (42.1)	111 (38.1)	155 (45.3)
Age 12, n (%)				298 (33.7)	121 (28.8)	177 (38.1)
Age 8, n (%)				102 (5.3)	65 (21.5)	95 (28.8)

α: N smaller than indicated in some variables due to missing values

Table 2. Distribution of age, height, weight, body mass index, FEV_1 and FVC for the two study populations.[α]

	Cross-sectional analyses population			Longitudinal analyses population		
	Total (N=721)	**Boys (N=338)**	**Girls N=(383)**	**Total (N=915)**	**Boys (N=434)**	**Girls (N=481)**
16 years						
Age (years), mean (SD)	16.3 (0.2)	16.3 (0.2)	16.3 (0.2)	16.3 (0.2)	16.3 (0.2)	16.3 (0.2)
Weight (kg), mean (SD)	64.2 (10.1)	68.1 (10.1)	60.7 (8.8)	64.1 (10.0)	67.8 (9.9)	60.9 (8.8)
Height (cm), mean (SD)	175.5 (8.6)	181.7 (6.7)	169.9 (6.0)	175.3 (8.5)	181.5 (6.4)	170.0 (6.0)
BMI (kg/m^2), mean (SD)	20.8 (2.7)	20.6 (2.7)	20.9 (2.6)	20.8 (2.6)	20.5 (2.6)	21.0 (2.6)
FEV_1 (L), mean (SD)	3.92 (0.70)	4.43 (0.62)	3.48 (0.44)	3.92 (0.70)	4.43 (0.62)	3.50 (0.44)
FVC (L), mean (SD)	4.70 (0.85)	5.35 (0.69)	4.15 (0.51)	4.70 (0.85)	5.35 (0.69)	4.15 (0.51)
12 years						
Age (years), mean (SD)				12.6 (0.3)	12.6 (0.3)	12.6 (0.3)
Weight (kg), mean (SD)				48.2 (9.1)	47.6 (9.2)	48.8 (8.9)
Height (cm), mean (SD)				160.0 (7.5)	159.5 (7.8)	160.5 (7.2)
BMI (kg/m^2), mean (SD)				18.7 (2.6)	18.6 (2.6)	18.8 (2.6)
FEV_1 (L), mean (SD)				2.71 (0.42)	2.69 (0.44)	2.72 (0.41)
FVC (L), mean (SD)				3.22 (0.51)	3.25 (0.51)	3.20 (0.50)
8 years						
Age (years), mean (SD)				8.1 (0.3)	8.0 (0.3)	8.1 (0.3)
Weight (kg), mean (SD)				29.0 (4.7)	29.0 (4.4)	29.0 (4.9)
Height (cm), mean (SD)				133.1 (5.6)	133.4 (5.4)	132.9 (5.7)
BMI (kg/m^2), mean (SD)				16.3 (1.8)	16.2 (1.7)	16.3 (1.9)
FEV_1 (L), mean (SD)				1.79 (0.24)	1.82 (0.24)	1.76 (0.23)
FVC (L), mean (SD)				2.01 (0.28)	2.06 (0.28)	1.96 (0.28)

α: N smaller than indicated in some variables due to missing values

Table 3. Distribution of annual average exposure concentrations for time windows of exposure and short-term exposures (cross-sectional analyses population, N=721)

	Min	Median	Mean (SD)	IQR	75th Percentile	Max
Preschool						
NO_2 ($\mu g/m^3$)	10.3	21.5	21.3 (5.5)	7.4	24.8	44.4
$PM_{2.5}$ absorbance ($10^{-5}/m$)	0.8	1.2	1.2 (0.2)	0.3	1.2	2.1
$PM_{2.5}$ ($\mu g/m^3$)	14.9	16.4	16.2 (0.7)	1.2	16.6	19.4
PM_{10} ($\mu g/m^3$)	23.7	24.4	24.6 (0.7)	0.9	24.8	28.6
PM_{coarse} ($\mu g/m^3$)	7.5	8.1	8.2 (0.5)	0.5	8.3	11.1
Primary school						
NO_2 ($\mu g/m^3$)	10.3	20.9	20.7 (5.2)	7.6	24.3	44.4
$PM_{2.5}$ absorbance ($10^{-5}/m$)	0.8	1.1	1.1 (0.2)	0.3	1.2	1.9
$PM_{2.5}$ ($\mu g/m^3$)	14.9	16.4	16.2 (0.7)	1.2	16.6	19.4
PM_{10} ($\mu g/m^3$)	23.7	24.3	24.5 (0.7)	0.8	24.8	28.5
PM_{coarse} ($\mu g/m^3$)	7.5	7.9	8.1 (0.4)	0.5	8.3	10.7
Secondary school						
NO_2 ($\mu g/m^3$)	10.3	20.9	20.6 (5.3)	7.9	24.3	44.4
$PM_{2.5}$ absorbance($10^{-5}/m$)	0.8	1.1	1.1 (0.2)	0.3	1.2	1.8
$PM_{2.5}$ ($\mu g/m^3$)	14.8	16.4	16.2 (0.6)	1.2	16.6	18.7
PM_{10} ($\mu g/m^3$)	23.7	24.3	24.5 (0.7)	0.8	24.7	27.7
PM_{coarse} ($\mu g/m^3$)	7.5	7.9	8.1 (0.4)	0.5	8.3	10.7
Short term exposures$^{\alpha}$						
NO_2	24.1	14.7	15.9 (6.8)	9.6	20.1	42.7
PM_{10}	8.3	15.8	18.5 (7.0)	6.8	20.3	46.5

α :Average concentrations for the 7 days preceding the 16-year lung function measurement

IQR = interquartile range

Table 4. Additionally adjusted associations of preschool time window average air pollution exposure with lung function growth from age 8 to 16 (N=871)[α]

	Increment	**Difference in FEV_1 % (95% CI)**	**Difference in FVC % (95% CI)**
NO_2	7.8 µg/m^3	-0.31 (-0.47 to -0.14)	0.01 (-0.14 to 0.16)
$PM_{2.5}$ absorbance	0.3 10^{-5}/m	-0.33 (-0.51 to -0.16)	0.05 (-0.11 to 0.22)
$PM_{2.5}$	1.2 µg/m^3	-0.26 (-0.49 to -0.03)	0.24 (0.03 to 0.45)
PM_{10}	0.9 µg/m^3	-0.20 (-0.33 to -0.08)	-0.02 (-0.13 to 0.09)
PM_{coarse}	0.5 µg/m^3	-0.17 (-0.28 to -0.06)	-0.01 (-0.11 to 0.09)

α: Estimates interpreted as the percent difference in 1-year growth (95% confidence intervals) in FEV_1 (FVC) for an interquartile range (IQR) increase in exposure. Adjusted for sex, age, and log-transformations of weight, and height, parental education, maternal atopy, paternal atopy, breastfeeding, respiratory infections in the last 3 weeks (prior to the medical examination), Dutch nationality, indoor tobacco smoke exposure in the home at 3 months, maternal smoking in pregnancy, furry pets in the home at 3 months, mould in the home at 1 year, gas cooking at 3 months, and average air pollution concentrations for the 7 days preceding the lung function measurement. N smaller than indicated due to missing values.

ABBREVIATIONS

BAMSE:	Children, Allergy, Milieu, Stockholm, Epidemiological Survey
CI:	Confidence interval
$FEV_{1:}$	Forced expiratory volume in 1 second
FVC :	Forced vital capacity
GINI :	German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development
LISA	Influence of Life style factors on the development of the Immune System Allergies in East and West Germany plus the influence of traffic emissions and genetics
LUR:	Land-use regression
NO_2:	Nitrogen dioxide
NO_x:	Nitrogen oxides
PIAMA:	Prevention and Incidence of Asthma and Mite Allergy
PM_{coarse}:	Particulate matter (aerodynamic diameter between 2·5-10 µm)
PM_{10}:	Particulate matter (aerodynamic diameter <10µm)
$PM_{2·5}$:	Particulate matter (aerodynamic diameter <2·5µm)
$PM_{2·5}$ absorbance:	Reflectance of $PM_{2·5}$ filters

FIGURES

Figure 1. Correlation between measurements from the first comparison series: Masterscreen IOS and EasyOne1 spirometer (upper panels) and the second series:EasyOne1 spirometer from the first series to another EasyOne2 spirometer of the same generation (lower panel).

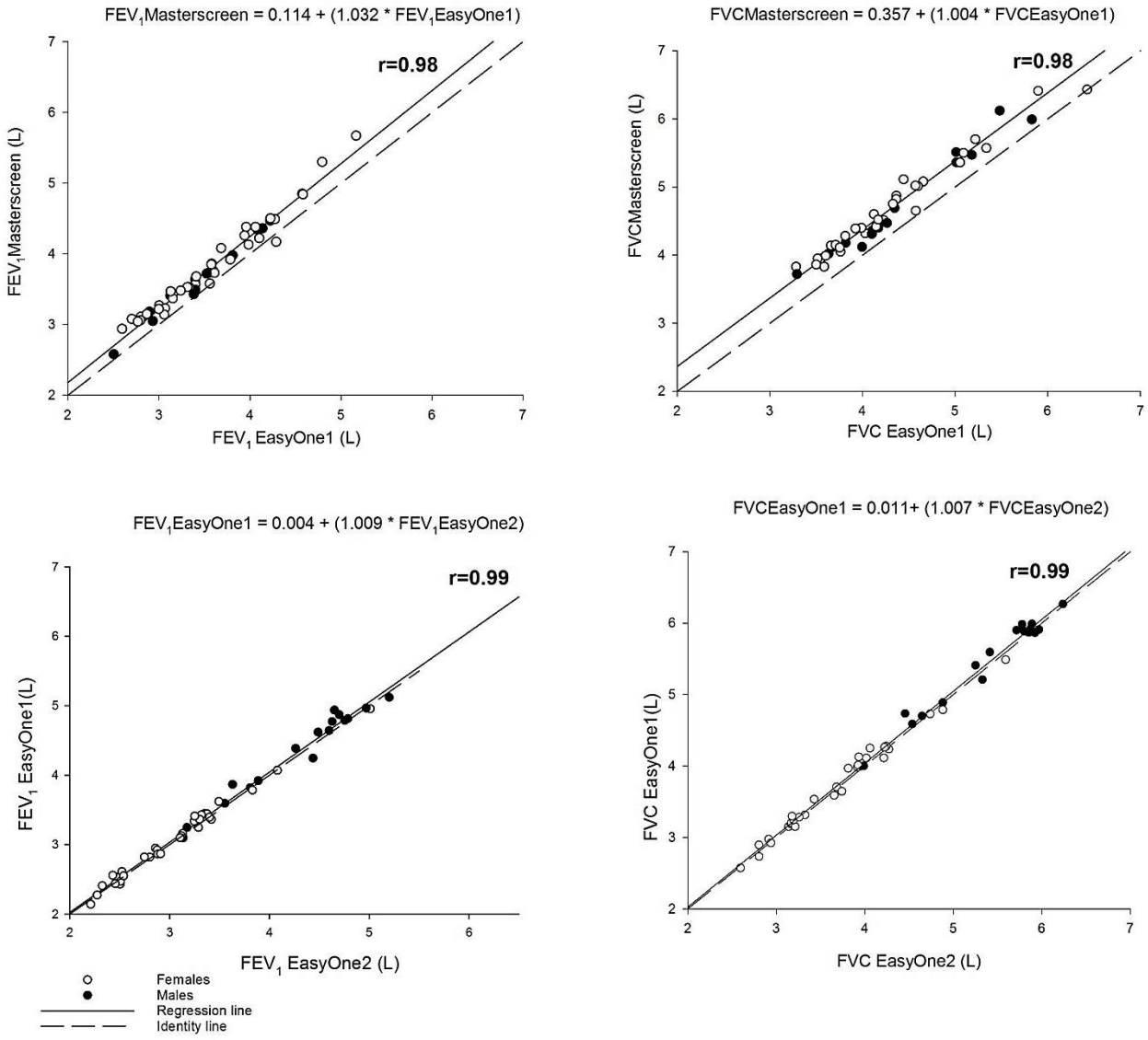
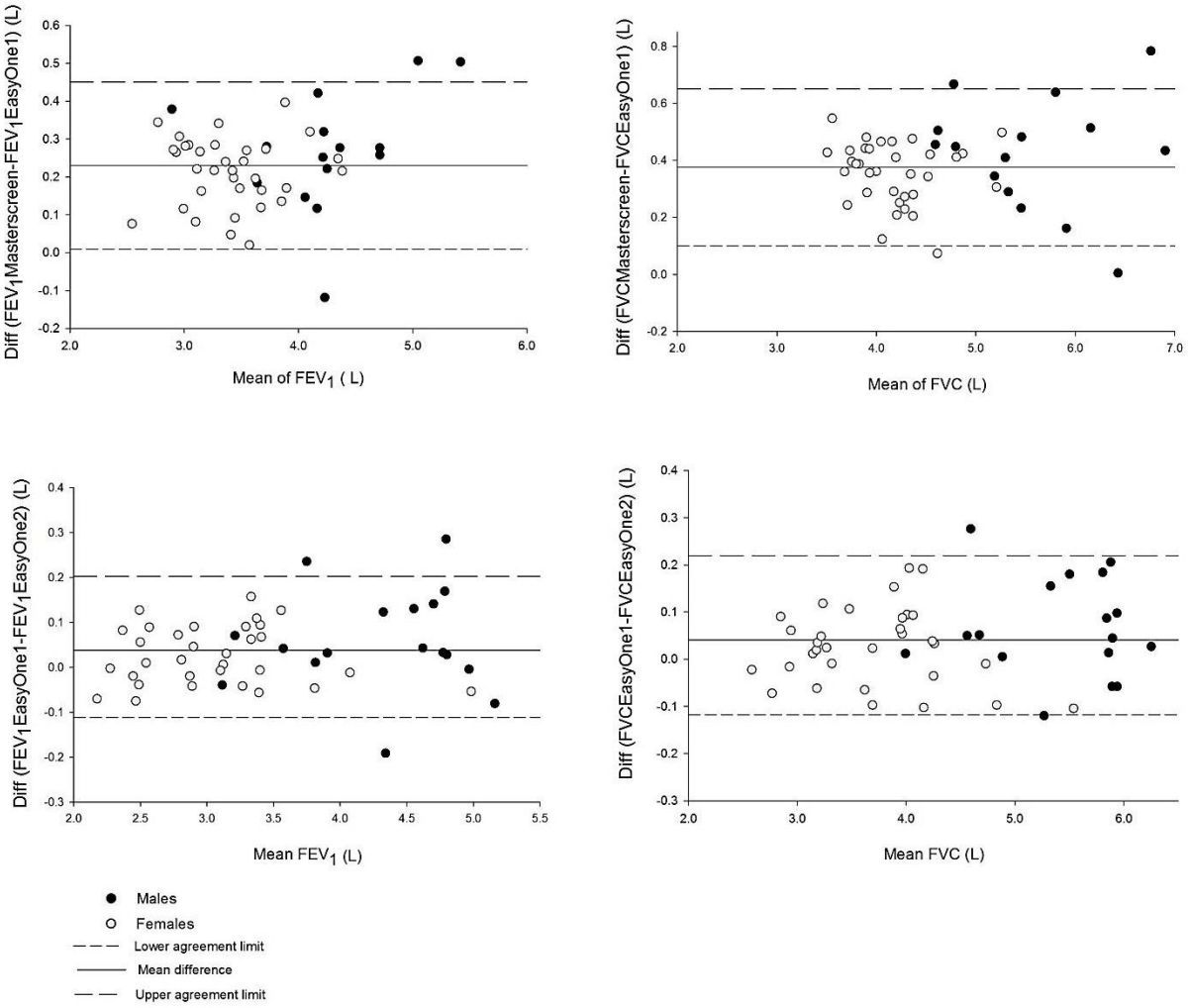
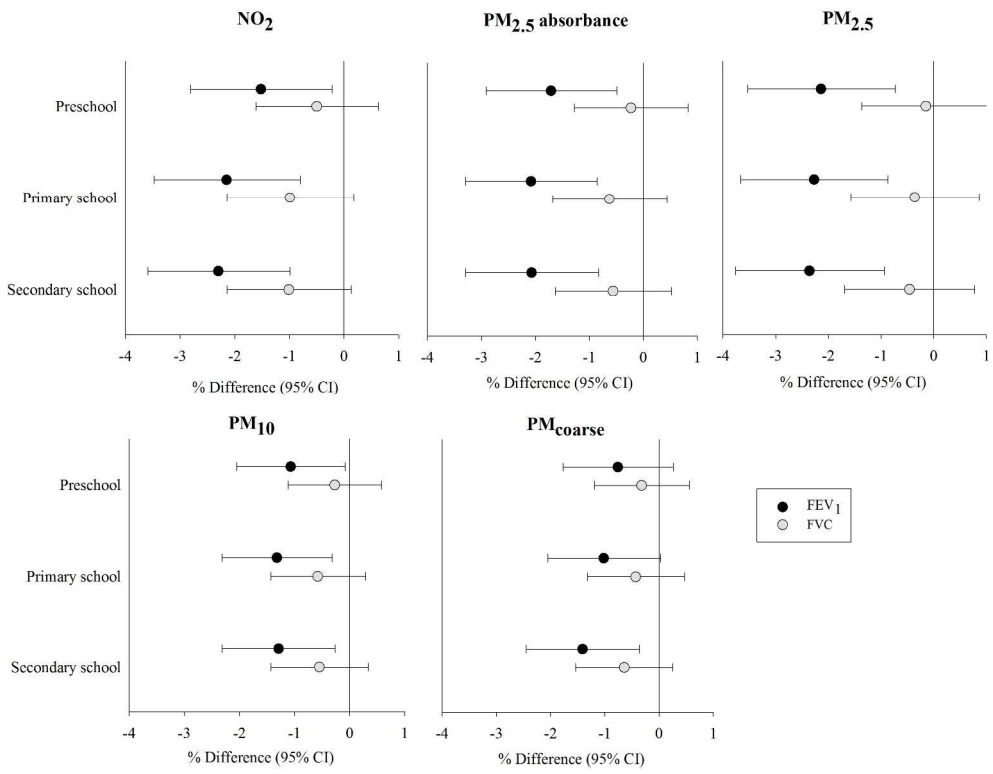
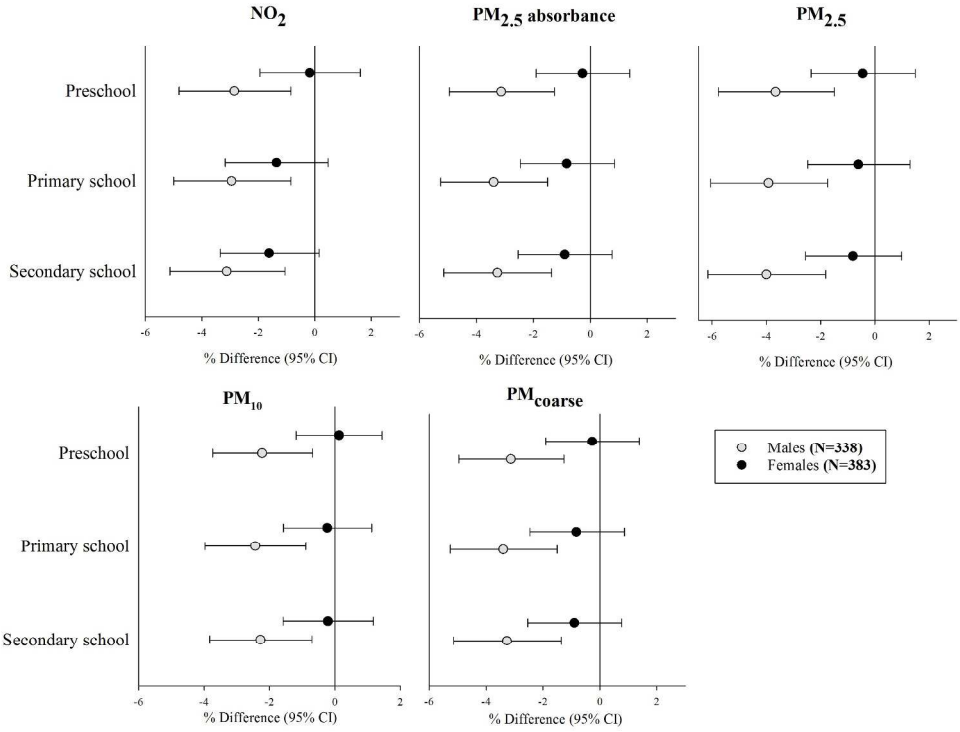


Figure 2. Bland and Altman plots of FEV_1 and FVC measurements from the first test series: Masterscreen IOS and EasyOne1 spirometer (upper panels) and the second test series:EasyOne1 spirometer from the first series to another EasyOne2 spirometer of the same generation (lower panel).





Additionally adjusted associations of time window average air pollution exposure with lung function at age 16 (N=674).┼ ┬ Adjusted for sex, age, log-transformations of weight and height, parental education, maternal atopy, paternal atopy, breastfeeding, respiratory infections in the last 3 weeks, Dutch nationality, indoor tobacco smoke exposure in the home at 3 months, maternal smoking in pregnancy, furry pets at 3 months, mould in the home at 1 year, gas cooking at 3 months, and average air pollution concentrations for the 7 days preceding the lung function measurement.
Exposure increments: 7.8 µg/m3 for NO2, 0.3 10-5/m for PM2.5 absorbance, 1.2 µg/m3 for PM2.5, 0.9 µg/m3 for PM10 and 0.5 µg/m3 for PMcoarse. ┼ ┬



Additionally adjusted association of time window average air pollution exposure with FEV1 at age 16 stratified by sex.├ ┬ Adjusted for age, log-transformations of weight and height, parental education, maternal atopy, paternal atopy, breastfeeding, respiratory infections in the last 3 weeks, Dutch nationality, indoor tobacco smoke exposure in the home at 3 months, maternal smoking in pregnancy, furry pets at 3 months, mould in the home at 1 year, gas cooking at 3 months, and average air pollution concentrations for the 7 days preceding the lung function measurement.
Exposure increments: 7.8 µg/m3 for NO2, 0.3 10-5/m for PM2.5 absorbance, 1.2 µg/m3 for PM2.5, 0.9 µg/m3 for PM10 and 0.5 µg/m3 for PMcoarse. ├ ┬